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Fibromyalgia and the painful self: A meta-analysis of resting-state fMRI data

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ABSTRACT

Fibromyalgia (FM) is a complex medical condition. The nested hierarchical model of self and its extension to the pain matrix could represent an integrated theoretical framework that might comprehensively captures FM clinical feautres. A multi-level meta-analysis was conducted. Resting-state functional connectivity (RS-FC) studies that compared patients with FM and healthy controls (HCs) were included. The association between RS-FC among self-related brain regions and pain intensity was also explored in the FM group. Eleven studies were eligible for meta-analytic procedures. Patients with FM, compared to HCs, were characterized by an increased RS-FC between the default mode network (DMN) and areas ascribed to interoceptive (e.g., insula) and exteroceptive (e.g., premotor, visual/auditory cortices) self layers. The clinical group also showed a reduced RS-FC among regions of the pain matrix (i.e., periaqueductal gray matter, somatosensory areas) involved in pain modulation. An increased RS-FC within DMN together with a heightened RS-FC between DMN and interoceptive self areas were positively associated to pain intensity reported by patients with FM. The nested hierarchical model of self and its extension to the pain matrix might represent comprehensive neurobiological backgrounds for clarifying core mind-body clinical features of FM.

1. Introduction

Fibromyalgia (FM) is a chronic syndrome characterized by widespread musculoskeletal pain associated to fatigue, non-restorative sleep, and cognitive deficits (Wolfe et al., 2016) with a higher incidence among women (Branco et al., 2010). Furthermore, FM highlights high co-occurrence rates with other pain-related and non-rheumatic diseases (e.g. neurological, gastrointestinal, endocrine) (Fitzcharles et al., 2018). Core clinical features of FM also encompass psychopathological manifestations together with significant alterations of psychological and affective functioning.

Specifically, a recent systematic review (Kleykamp et al., 2021) showed that up to 50% of FM patients met a lifetime diagnosis of major depression disorder (MDD), which represents the most prevalent co-occurring mental disorder. Additional psychiatric comorbidities refer to post-traumatic stress disorder (PTSD) (lifetime: 16.1%; current: 39.1%), personality disorders (current: 19.3%) and panic disorders (lifetime: 33.0%; current: 11.6%). Considering subjective experiences of patients with FM, it has been suggested that their sense of self is "entrapped" in present-moment painful symptoms (Hellström et al., 2001). Moreover, physical pain significantly affects anticipations of future self representation and related phenomena (e.g., affective reactions, expectations, beliefs) (Hellström, 2001). Accordingly, it has been developed the concept of "self-pain enmeshment" (Morley et al., 2005; Pincus et al., 2001) that is captured by the degree of overlap among three domains of psychological functioning: i) the *pain schemas* includes properties of pain experiences. The pain schemas is also involved in the engagement in self-protective behaviors (e.g., escape),

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which interrupt ongoing goal-oriented behaviors; ii) the *illness schemas* contains information about the affective and behavioral consequences of illnesses, such as implications for autonomous functioning, goal achievement and quality of life; iii) the *self schemas* is characterized by a hierarchical and dynamic organization of information about personal characteristics and behavioral repertories across different contexts and over time. The higher is the degree of overlap among these schemas, the higher is psychological suffering and related maladjustment among patients with FM (Pincus et al., 2001).

Furthermore, empirical research has supported relevant implications of several emotion-related processes for FM clinical manifestations. The most investigated constructs among patients with FM refer to alexithymia — difficulty in identifying and describing subjective feelings, distinguishing between feelings and the bodily sensations of emotional arousal (Taylor et al., 1997) — and emotion regulation — processes involved in influencing positive and negative emotions consciously or automatically, in terms of intensity, duration, and/or quality (Naragon-Gainey et al., 2017). Particularly, a recent meta-analysis (Habibi et al., 2023) showed that patients with FM highlighted higher levels of alexithymia (i.e., large effect sizes) than healthy controls (HCs) and other pain-related conditions (i.e., small-to-moderate effect sizes). Interestingly, levels of alexithymia positively correlated with the severity of pain and anxiety/depression symptoms reported by subjects with FM. Similarly, empirical evidence suggested that patients with FM reported widespread difficulties with emotion regulation, which were characterized by a recurrent use of maladaptive strategies (e.g., expressive suppression; for a review see: Koechlin et al., 2018). Furthermore, provisional results among different FM samples found significant relationships between the use of expressive suppression (i.e., positive) and cognitive reappraisal (i.e., negative) with the intensity of pain symptoms (Koechlin et al., 2018). It has been also suggested that interoception — processing and perception of inner bodily signals (Cameron, 2001; Craig, 2002) — represents a prerequisite for emotion regulation processes and a protective factor alexithymia (Zamariola et al., 2019). Interestingly, interoception has been widely explored among patients with FM. Particularly, several studies (e.g., Duschek et al., 2017; Todd et al., 2024; Schmitz et al., 2021; Valenzuela-Moguillansky et al., 2017) consistently identified alterations of self-report measures (e.g., low awareness of body sensations; experiencing one's body as unsafe and untrustworthy) and task-dependent performances (e.g., reduced accuracy of heartbeat counting) assessing interoceptive processes. Moreover, these studies showed that deficits with interoception positively correlated with the severity of FM symptoms.

According to this evidence, FM might be viewed as a complex medical condition in which core pain-related symptoms shape patients' self representation. Altered affective processes (e.g., deficits with interoception, alexithymia and dysfunctional emotion regulation strategies) play a role in reinforcing FM pain-related symptoms. The implications of these psychological mechanisms for FM clinical manifestations could be also involved in explaining the high co-occurrence rates with psychiatric disorders characterized by high levels of internalized negative affectivity (e.g., MDD, PTSD) (Kotov et al., 2021; Ringwald et al., 2023). Despite this evidence, there is a lack of a conceptual framework that could help study the complexity of this medical condition from a comprehensive mind-body connection perspective.

1.1. The nested hierarchy of self and its affective regulatory processes: implications for FM

The concept of self and its neurobiological underpinnings could represent a promising approach in order to understand FM and related core features within an integrated mind-body conceptual framework. Departing from a neuroscience perspective, it has been suggested that activity of cortical midline structures (Northoff and Bermpohl, 2004), including the Default Mode Network (DMN), are associated to a self-related processing of internal and external stimuli (Buckner et al., 2008; Raichle et al., 2001). Furthermore, the DMN has been associated to self-related spontaneous thoughts during the resting state (Huang et al., 2016; Scalabrini et al., 2018). This has suggested how information related to the self: i) overlap with the resting state; ii) are contained in the spontaneous neural activity; iii) might provide the basis for the emergence of different kind of mental contents, including affective states together with cognitive, social and sensorimotor functions (Huang et al., 2016; Scalabrini et al., 2018).

Following this approach, the self has been conceptualized as a "fundamental reference" or a "psychological baseline" for processing internal signals and external environmental inputs (Northoff, 2016; Northoff and Bermpohl, 2004; Northoff et al., 2022, 2022; Scalabrini et al., 2021a; 2022). This conceptualization of the self has found a solid support from neuroscience data that have suggested a nested hierarchical organization of self-related processes (Qin et al., 2020). According to empirical findings, a large-scale meta-analysis (Qin et al., 2020) among healthy subjects has been identified three layers.

(i) *interoceptive self* refers to the processing of the body's inner organs relative to the incoming exteroceptive stimuli. The interoceptive self has been related to the bilateral insula, dorsal anterior cingulate cortex (dACC), thalamus, and parahippocampus activities;
(ii) *extero-proprioceptive self* focuses on external or proprioceptive bodily inputs. The extero-proprioceptive self has been linked to the bilateral insula, inferior frontal gyrus (IFG), premotor cortex, temporo-parietal junction (TPJ) responses. Visual and auditory cortices have been also considered secondary regions involved in exteroceptive self-processing mechanisms (Qin et al., 2020; Scalabrini et al., 2020);
(iii) *mental self* considers the inner cognitive activity in terms of self-related stimuli vs. non-self ones. The mental self has been associated to the DMN, including the medial prefrontal cortex (MPFC) and posterior cingulate cortex. Interestingly, it also includes regions from the extero-proprioceptive self (i.e., bilateral TPJ), and those related to the interoceptive self (i.e., bilateral insula, thalamus).

According to these findings, regions of the interoceptive self represent the foundations of the other layers (extero-proprioceptive and mental self). Extero-proprioceptive and mental layers are complemented by additional regions extending the topography of the self and its nestedness. The insula represents the common denominator of the three networks (Scalabrini et al., 2021b).

Intriguingly, a nested hierarchical neural organization has been replicated for relevant affective-related processes involved in FM clinical features, such as interoception and high-order emotion regulation strategies. Departing from the centrality of interoception for self-regulation of affective states (Barrett et al., 2004), Tan and colleagues (2022) conducted an extensive meta-analytic review of task-dependent fMRI studies investing brain activity associated to interoception (e.g., heartbeat counting/monitoring; breath monitoring tasks), and emotion regulation (e.g., reappraisal, suppression). According to theoretical conceptualizations (Barrett et al., 2004), interoception represented the most basic level of affective-related functioning and it was associated to the bilater insula and dACC. These results fully overlapped with interoceptive self-processing layer. The meta-analysis of emotion regulation studies found regions associated to interoception (i.e., insula, dACC) together with other key regions, namely the caudate and TPJ. This evidence suggested a partial overlap between emotion regulation processes and the extero-proprioceptive self-processing layer.

Ultimately, it has been hypothesized that a well-known extended brain network called as the "pain matrix" (Baliki et al., 2015) might be involved in core pain-related symptoms associated to FM (e.g., allodynia, hyperalgesia) (Garcia-Larrea and Peyron, 2013). Looking at the "pain matrix", hundreds of studies have identified that acute or transient painful experiences are associated to the activity of the thalamus, primary and secondary somatosensory areas (SSAs), insula, ACC, and periaqueductal gray matter (PAG) (Geha and Waxman, 2016). This areas are also functionally connected to anterior and posterior portions of the DMN (e.g., Alshelh et al., 2018; Kim et al., 2019; Kucyi et al., 2013) and limbic regions (e.g., amygdala) (Čeko et al., 2020; Veinante et al., 2013). Moreover, it has been shown that the pain intensity correlates with neural response magnitude within areas of the pain matrix, especially the insula and ACC (Frediani and Bussone, 2019).

Interestingly, the "pain matrix" seems to partially overlap with brain networks associated to self-processing layers. Indeed, pain experiences are processed by areas of interoceptive (i.e., insula, ACC, thalamus) and mental (i.e., DMN) self layers. Whereas, specific "pain matrix" areas, especially the SSAs and PAG, might extent the topographical neural organization of self-processing layers linked to pain-related phenomena. Indeed, it has been suggested that the PAG might be involved in processing of basic affective and somatosensory self-related experiences (i.e., "proto-self"; Northoff and Panksepp, 2008; Panksepp and Northoff, 2009).

Therefore, these neuroscience findings might suggest that the complex mind-body clinical features of FM are related to a nested hierarchical organization of neural networks capturing different self layers. Specifically, intero-exteroceptive and mental self layers together with pain matrix areas (i.e., SSAs, PAG, limbic) might represent the foundations for emotional and physical pain-related experiences characterizing FM patients. Intero-exteroceptive self layers might also play a role in alterations of affective-related processes (i.e., interoception, emotion regulation) recurrently reported by patients with FM. Furthermore, brain areas of the pain matrix (i.e., SSAs and PAG) could be specifically involved in the modulation of painful experiences (Gamal-Eltrabily et al., 2021) representing core symptoms of FM. These considerations might suggest an extension of the topography of self and its nestededness in relation to mind-body pain-related phenomena (see Table 1 for a summary). Nevertheless, there are no studies that have quantitatively summarized neuroscience evidence among patients with FM in the light of this evidence-based neuroscience theoretical perspective.

1.2. *The current study*

Departing from these theoretical considerations, the current study aims at conducting a quantitative meta-analysis of fMRI data that compared resting-state (RS) functional connectivity (FC) neural activity between patients with FM and HCs. The RS-FC was chosen for two main reasons. First of all, there is a wide consensus in considering spontaneous RS activity as a valid proxy for studying neural underpinnings of self organization (e.g., Scalabrini et al., 2019; Schneider et al., 2008; Qin and Northoff, 2011; Wicker et al., 2003). Secondly, the inclusion of RS-FC studies allowed to control possible sources of heterogeneity across studies sustaining the comparability of results. Considering the lack of prior quantitative works on this topic, we adopted an explorative approach with no specific a priori hypothesis concerning alterations of RS-FC among different brain regions associated to self layers and pain matrix. Furthermore, we explored associations between altered RS-FC among self and pain matrix areas with intensity of pain symptoms reported by patients with FM. This should represent a further support for the implication of the nested hierarchical model of self and its extension for core clinical features of FM.

2. Methods

2.1. *Criteria for selecting studies*

This meta-analysis was conducted referring to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; see supplementary materials) guidelines (Moher et al., 2009; Page et al., 2021). Fig. 1 shows the flow chart for the inclusion of studies. The analysis considered studies published in scientific journals in order to support their quality. Scopus, PubMed, PsychINFo, ISI Web of Knowledge, and online databases were used for the research. F.N and F.G. conducted the online research. The online research was based on the following keywords: "Fibromyalgia" AND "functional magnetic resonance OR fMRI" AND "resting-state OR resting state connectivity OR functional connectivity". In order to be included in the current meta-analytic review, the studies met the following inclusion criteria to support both the validity and the reliability of results: a) all studies admitted patients who met a diagnosis of FM according to the American College of Rheumatology; b) all studies compared RS-FC neural activity between patients with FM and HCs, c) all studies excluded subjects with FM affected from other chronic pain-related conditions, rheumatic and neurological diseases; d) HCs were not affected from FM, chronic pain-related conditions, rheumatic and neurological diseases together with psychiatric disorders; e) the assessment of pain and other psychopathological (i.e., depression and anxiety) symptoms was supported by valid and reliable instruments (see Table 2 for a description). Gender and age were not considered exclusion criteria of the study. According to the high co-occurrence rate of psychiatric disorders, especially MDD, these comorbidities were not considered exclusion criteria of this meta-analysis. However, it was estimated moderating effects on effect sizes (ESs) of gender distribution, age and the explicit exclusion of FM

Table 1
Overlaps among brain networks relevant for FM.

	Self			Affect self-regulation		Pain matrix
Brain regions	Interoceptive Self	Extero-proprioceptive Self	Mental Self	Interoception	Emotion regulation	Pain experiences and its modulation
Insula	■	■	■	■	■	■
Dorsal anterior cingulate cortex	■			■	■	■
Thalamus	■		■			■
Parahippocampus	■					
Inferior frontal gyrus		■				
Premotor cortex		■				
Temporo-Parietal Junction		■	■		■	
Anterior DMN			■			■
Posterior DMN			■			■
Somatosensory areas						■
Periaqueductal gray matter	■					■
Limbic areas						■

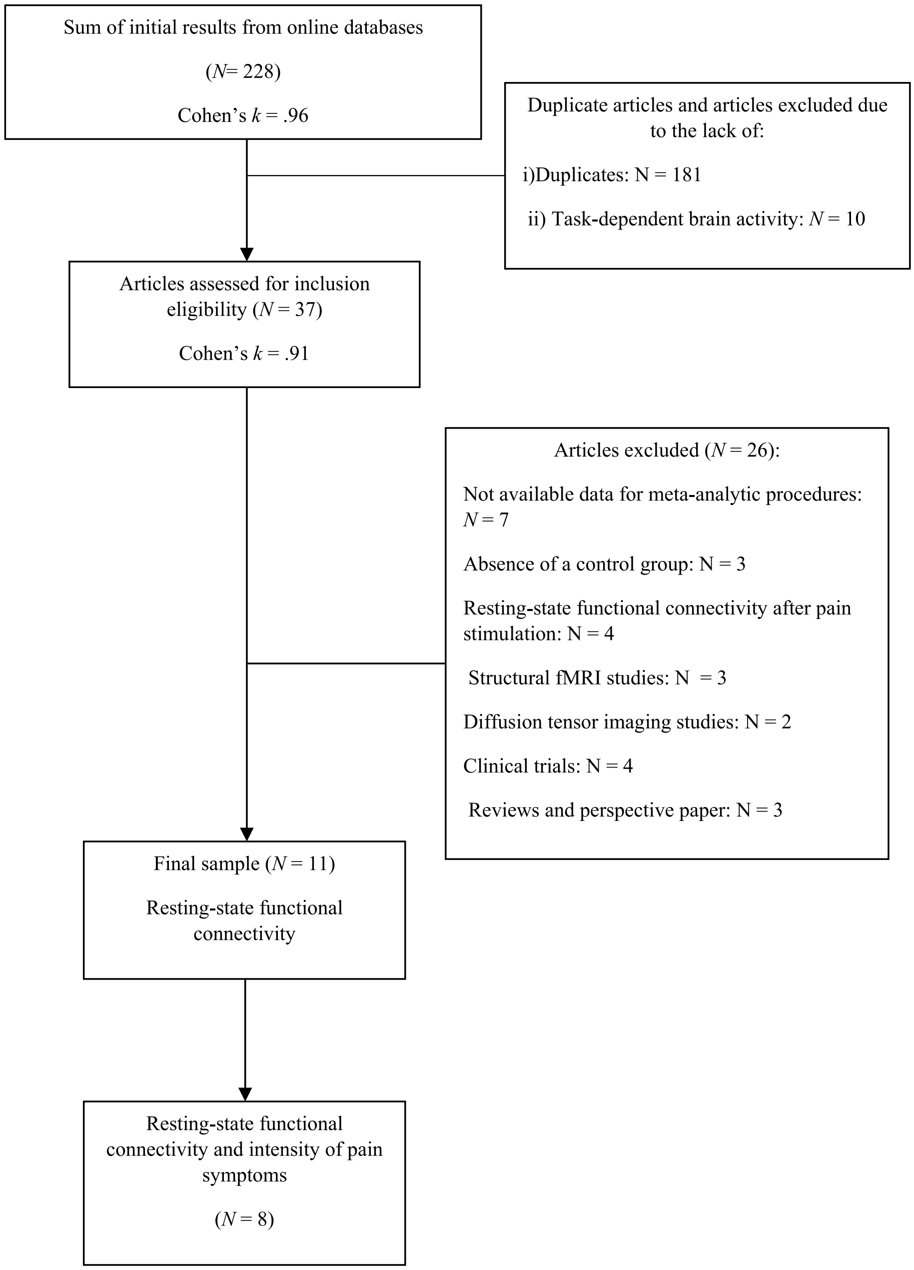

Fig. 1. CONSORT flow chart of studies inclusion process.

patients with co-occurring mental disorders.

A reliable initial sample of articles was guaranteed through a double-checked screening process. M.C and F.G. focused the screening process departing from articles that showed, within the abstract section, at least a RS-FC analysis among FM patients. Cohen *k* inter-rater reliability index (Cohen, 1960) was calculated for the studies selected.

2.2. Data analyses

Looking at RS-FC among self-processing areas and pain matrix, comparisons between FM patients and HCs were based on Cohen's *d* (Cohen, 1992) that was computed as an ES measure. The index was primarily calculated using descriptive statistics reported in the Results section of each study. Moreover, *t* and *z* values together with Pearson correlation coefficient (*r*) were used to estimate Cohen's *d* when descriptive statistics were not available. The suitable procedures proposed by Wolf (1986) together with Borenstein and colleagues (2011) were adopted to convert the previous indexes to Cohen's *d*. Whenever studies reported descriptive statistics, Cohen's *d* was also computed in order to highlight the extent of differences between FM patients and HCs in levels of depressive and anxious symptoms. Values of Cohen's *d* greater than or equal to .20, .50, and .80 were interpreted as small, moderate, and large ESs, respectively (Cohen, 1992). Whereas, the *r* coefficient was considered as an ES measure for testing the association between alterations of RS-FC and pain intensity among FM patients. Values of *r* greater than or equal to .10, .30, and .50 were interpreted as small, moderate, and large ESs, respectively (Cohen, 1992).

A multi-level meta-analysis was conducted using the {metafor} *R* package in order to adequately estimate the pooled ES (d_{pooled}) controlling for interrelationships among multiple ESs calculated within the same study (for a detailed description of statistical procedures see: Viechtbauer, 2010). The estimation of model parameters was based on the restricted maximum likelihood method (Harrer et al., 2021). The 3-level meta-analysis posited that ESs (level 2) were aggregated within

Table 2
Characteristics of studies included.

Study	Country	Sample size	Gender	Mean of age	Resting-state acquisition	Seed region	Regions of interest	Assessment of FM	Assessment of pain	Assessment of depressive symptoms	Assessment of anxiety symptoms	Psychiatric comorbidity
Pujol et al. (2014)	Spain	76 FM: 40 HC: 36	W	45.2 FM: 46.4 HC: 44.0	6 min	PAG SSAs	INT EXT DMN SSAs LIM	The American College of Rheumatology criteria for fibromyalgia	101-point numerical rating scale	HADS $d = 1.73$ [1.24–2.22]	HADS $d = 1.52$ [1.03–2.01]	Not reported
Čeko et al. (2020)	USA-Canada	32 FM: 16 HC: 16	W	47.9 FM: 47.8 HC: 48.0	6 min	DMN	INT	The American College of Rheumatology criteria for fibromyalgia	0–10 numerical rating scale	HADS $d = .94$ [.22–1.66]	HADS $d = 1.43$ [.67–2.19]	None Mental disorders were considered exclusion criteria including MDD
Flodin et al. (2015)	Sweden	25 FM: 14 HC: 11	W	45.1 FM: 48.4 HC:41.8	Not reported	INT SSAs	EXT SSAs	The American College of Rheumatology criteria for fibromyalgia	FIQ	–	–	Not reported
Napadow et al. (2010)	USA	36 FM:18 HC:18	W	37.5 FM: 38.9 HC:36.1	6 min	DMN	INT SSAs	The American College of Rheumatology criteria for fibromyalgia	Visual analog scale of 0–10	CES-D Values were not reported	HADS Values were not reported	None Mental disorders were considered exclusion criteria including MDD
Pando-Naude et al. (2019)	Mexico	40 FM: 20 HC: 20	W	44.3 FM:46.4 HC: 42.2	4.5 min	DMN	INT EXT SSAs	The American College of Rheumatology criteria for fibromyalgia	Verbal rating scale (VRS)	CES-D $d = 1.75$ [1.01–2.49]	STAI $d = 1.91$ [1.17–2.65]	Not reported
Flodin et al. (2014)	Sweden	38 FM: 16 HC: 22	W	47.0 FM:48.3 HC: 45.7	Not reported	INT SSAs	EXT SSAs	The American College of Rheumatology criteria for fibromyalgia	100 mm horizontal visual analogue scale FIQ	–	–	Not reported
Fallon et al. (2016)	UK	31 FM: 16 HC: 15	W	39.0 FM: 38.5 HC: 39.5	20 min	DMN	INT LIM	The American College of Rheumatology criteria for fibromyalgia	FIQ	BDI $d = 1.81$ [.97–2.65]	–	Not reported
Coulombe et al. (2017)	Canada	39 FM: 23 HC: 16	W	50.3 FM:50.6 HC: 49.8	10.5 min	PAG	INT LIM	The American College of Rheumatology criteria for fibromyalgia	BPI FIQ	HADS HC data were not reported	HADS HC data were not reported	Not reported
Truini et al. (2016)	Italy	35 FM:20 HC: 15	M + W % W in FM 95% % W in HC 86.7%	46.5 FM: 47.5 HC: 45.5	Not reported	PAG	INT LIM	The American College of Rheumatology criteria for fibromyalgia	Visual analogue scale	ZSDS	ZSAS	None Mental disorders were considered exclusion criteria including MDD
van Ettinger-Veenstra et al. (2020)	Sweden	59 FM: 31 HC: 28	W	40.5 FM: 39.2 HC:42.6	10 min	SSAs	INT	The American College of Rheumatology criteria for fibromyalgia	Numeric rating scale (0–10)	HADS $d = 1.80$ [1.20–2.40]	HADS $d = 1.45$ [.80–2.05]	Not reported
Kong et al. (2021)	United States	39 FM: 20 N: 19	M + W % W in FM 95% % W in HC 94.7%	51.9 FM: 51.6 HC: 52.3	8 min	LIM	DMN	The American College of Rheumatology criteria for fibromyalgia	FIQ	BDI-II $d = .74$ [1.39 - .09]	–	Not reported

BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; DMN = Default Mode Network; EXT = Exteroceptive self areas; FIQ = Fibromyalgia Impact Questionnaire; FIQR = HADS = Hospital Anxiety and Depression Scale; INT = Interoceptive self areas; LIM = Limbic areas; PAG = Periaqueductal gray; SSAs = Somatosensory areas; STAI = State-Trait Anxiety Inventory; ZSAS = Zung Self-Rating Anxiety Scale ZSDS = Zung Self-Rating Depression Scale.

clusters composed of each study (level 3).

The Q statistic (Hedges and Olkin, 1985) and multi-level I^2 index (Cheung, 2014) were estimated in order to evaluate the heterogeneity in ESs. According to the multi-level version of I^2 index, the total heterogeneity was split into a within- (i.e. level 2) and between-study (level 3) variability. Following a multi-level approach, the Akaike (AIC) and Bayesian Information Criterion (BIC) indexes were used to compare the fit to data of the 2-level with the 3-level model through the application of a likelihood ratio test (LRT).

Three-level mixed-effect meta-regressions were computed in order to estimate the pooled ESs of the difference between FM and HCs in RS-FC neural activity within regions of interest related to self layers and the pain matrix. The Z-test procedure (Borenstein et al., 2011) was applied to compare the absolute value of significant pooled ESs reflecting differences in RS-FC neural activity between groups. This was conducted in order to estimate which RS-FC alteration might be the most representative of FM patients. An adequate Bonferroni's correction was applied for multiple comparisons.

The meta-regression was also conducted in order to evaluate possible moderating effects of: i) year of publication; ii) sample size; iii) gender (i.e., males + females vs only females); iv) age; v) psychiatric disorders as exclusion criteria of original study. Considering a subgroup of studies that allowed to estimate differences in levels of depressive and anxious symptoms between groups, multi-level meta-regressions were conducted in order to control possible effects of the severity of these symptoms on RS-FC alterations.

Egger's regression (Egger et al., 1997) was estimated to detect publication bias. Bootstrap methodology (i.e., bias corrected and accelerated; Davison and Hinkley, 1997) was applied in computing the significance of the previous parameter.

3. Results

3.1. Descriptive statistics

Eleven studies ($N_{ES} = 52$) (see Table 2 for a detailed description of characteristics of studies included) were eligible for a total of 454 subjects (FM = 236) with a mean age of 45.03 years old (SD = 4.47) (FM = 45.93 [4.49]). Studies that reported the duration of illness (N = 5) highlighted a mean of 8.54 years (SD = 1.82). Six studies allowed to estimate ESs of difference in depressive symptoms between FM and HCs. Specifically, FM subjects showed a very large difference in depressive symptoms than HCs ($d_{mean} = 1.46$ [SD = .51]); specifically, FM patients highlighted a more severe depressive symptomatology. Similar results were replicated for anxious symptoms (N = 4; $d_{mean} = 1.60$ [SD = .27]). Three studies explicitly declared that patients with FM were not affected from any psychiatric disorders due to the fact that they were considered as exclusion criteria of original research. Whereas, the remaining studies did not report any information about psychiatric comorbidities.

The seed regions used for RS-FC analysis were: i) the DMN (N = 4; 36.3%); ii) the PAG (N = 3; 27.2%); iii) interocpetive areas (i.e., insula and ACC) (N = 2; 18.1%); iv) SSAs (N = 1; 9.0%) and limbic areas (e.g., amygdala) (N = 1; 9.0%). Whereas, the regions of interests analyzed across studies were: i) interoceptive areas ($N_{ES} = 14$; 26.9%); ii) exteroceptive areas, including visual and auditory cortices ($N_{ES} = 12$; 23.1%); iii) SSAs ($N_{ES} = 10$; 19.2%); iv) limbic ($N_{ES} = 7$; 13.4%); iv) the DMN ($N_{ES} = 5$; 9.6%); v) executive frontal areas ($N_{ES} = 4$; 7.7%).

Eight studies ($N_{ES} = 20$) reported correlations between alterations of RS-FC and intensity of pain symptoms among patients with FM. The most investigated seed regions were: i) the DMN ($N_{ES} = 7$; 35.0%); ii) the PAG ($N_{ES} = 6$; 30.0%); iii) the SSAs ($N_{ES} = 4$; 20.0%); iv) the interoceptive areas (i.e., insula and ACC) ($N_{ES} = 3$; 15.0%).

3.2. Alterations of RS-FC

The 3-level model showed the best fit to data compared to the 2-level one ($\chi^2_{(1)} = 7.46$; $p < .01$). The analyses showed that patients with FM were characterized by a significant increased RS-FC between the DMN and exteroceptive ($d_{pooled} = 2.89$ [1.67–4.10]; p < .001) together with interoceptive ($d_{pooled} = 2.08$ [.73–3.43]; p < .01) self areas compared to HCs. Furthermore, the analyses highlighted a reduced RS-FC between the PAG and SSAs ($d_{pooled} = -1.37$ [−2.72 to −.02]; p < .05) among patients with FM compared to HCs. Comparing the absolute values of the previous pooled ESs, the analysis did not find significant difference among them. Meta-analytic procedures showed a significant heterogeneity ($Q_{(40)} = 272.13$; p < .001) of results within ($I^2 = 31.12\%$) and between ($I^2 = 59.08\%$) studies. The meta-regression analysis did not find significant moderators of ESs. Particularly, the analysis did not find a significant moderating effect of exclusion criteria of psychiatric disorders on ESs reflecting alterations of RS-FC among FM patients compared to HCs. Ultimately, Egger's regression highlighted bias of publication (Egger's coefficient: −2.36 [−3.71 to −.80]; p < .01). Fig. 2 graphically summaries the previously mentioned meta-analytic findings.

3.3. Effects of depressive and anxious symptoms on alterations of RS-FC

Looking at the impact of severity of depressive symptoms on the extent of alterations of RS-FC among FM patients (N = 6; $N_{ES} = 30$), meta-regression analysis did not find a significant relationship between this psychopathological dimension and ESs ($F_{(1, 28)} = .50$; *ns*). Furthermore, the severity of depressive symptoms did not explain the significant ($Q_{(28)} = 442.32$; p < .001) heterogeneity found within ($I^2 = 51.68\%$) and between ($I^2 = 42.84\%$) studies. Similarly, the severity of anxious symptoms (N = 4; $N_{ES} = 26$) was not related to ESs reflecting alterations of RS-FC ($F_{(1, 24)} = .32$; *ns*) and, it did not explain the heterogeneity of results ($Q_{(24)} = 267.18$; p < .001) within ($I^2 = 31.58\%$) and between ($I^2 = 63.98\%$) studies.

3.4. Association between alterations of RS-FC and pain intensity

The 3-level model showed the best fit to data compared to the 2-level one ($\chi^2_{(1)} = 11.09$; $p < .001$). The analysis found a significant and large association between the intensity of pain symptoms and increased RS-FC between the DMN (seed region) and interoceptive areas together with and increased intra DMN RS-FC ($r_{pooled} = .67$ [.29–1.05]; p < .01). Considering the absolute values, the relationship between pain intensity and increased RS-FC organized around the DMN activity was significantly larger than those centered on the PAG ($r_{pooled} = -.12$ [-.51 – .27], *ns*; Z = 2.17; p < .0167) and SSAs ($r_{pooled} = -.14$ [-.37 – .19], *ns*; Z = 2.17; p < .0167). The analyses showed a significant heterogeneity ($Q_{(16)} = 171.79$; p < .001) of results within ($I^2 = 11.36\%$) and between ($I^2 = 83.36\%$) studies. The meta-regression analysis did not find significant moderators of ESs. Ultimately, Egger's regression did not find significant bias of publication (Egger's coefficient: 1.19 [-.98 – 1.46]; ns).

4. Discussion

The current meta-analysis sought to provide a provisional support for a new comprehensive mind-body framework based on neuroscience evidence that could clarify neurobiological processes associated to core clinical features of FM taking into account physical, psychopathological and psychological domains. Accordingly, we used the nested hierarchical model of self (Qin et al., 2020) that might represent a solid framework to understand different core clinical characteristics of this syndrome. Furthermore, given the key role of chronic and widespread pain as a core symptom of FM, we included specific brain areas of the pain matrix (i.e., PAG, SSAs), which represents an extended brain network involved in sustaining painful experiences and their modulation. This was chosen departing from empirical evidence that has highlighted a partial overlap between the pain matrix network and self-processing layers (i.e., interoceptive and mental).

2a. Increased RS-FC among self-processing layers in FM patients compared to HCs

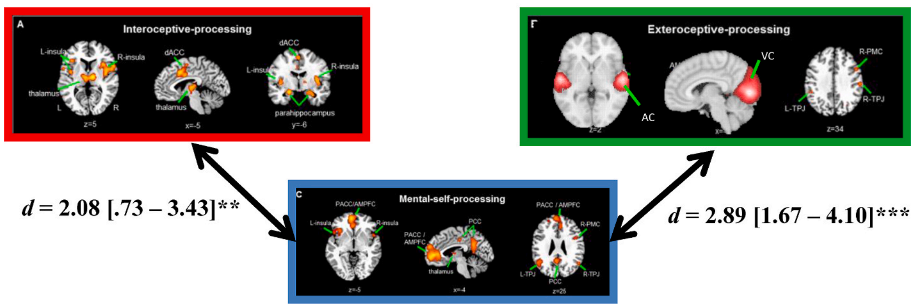

Fig. 2a. Increased RS-FC among self-processing layers in FM patients compared to HCs.

2b. Reduced RS-FC between PAG and SSAs (pain matrix) in FM patients compared to HCs

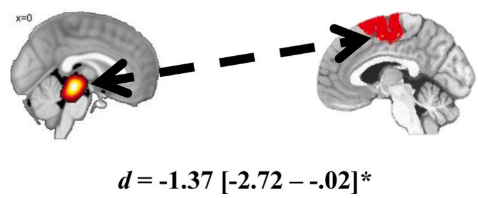

Fig. 2b. Reduced RS-FC between PAG and SSAs (pain matrix) in FM patients compared to HCs.

The current meta-analytic results showed 3 main findings.

i) patients with FM, compared to HCs, were characterized by an increased RS-FC between the DMN, which is a key region of the mental self layer, and areas ascribed to intero- and exteroceptive self layers;
ii) the clinical group, compared to the control one, showed a reduced RS-FC among key regions of the pain matrix (i.e., PAG and SSAs) involved in pain modulation;
iii) an increased intra DMN RS-FC together with an heightened RS-FC between the DMN and interoceptive self areas were positively associated to pain intensity reported by patients with FM.

First, the increased RS-FC among areas encompassing self layers seems to provide a support for the hypothesis that FM could be understood in the light of core alterations of mind-body self-processing mechanisms. Particularly, the heightened RS-FC between the DMN and interoceptive areas (i.e., insula and ACC) might support self-report and psychophysics findings that have highlighted a heightened interoceptive sensitivity and hyper-vigilance toward body signals among patients with FM compared to HCs (Duschek et al., 2017; Todd et al., 2024; Schmitz et al., 2021; Valenzuela-Moguillansky et al., 2017). This conclusion is supported by neuroscience data that found relevant implications of RS-FC among these areas for the previously mentioned mind-body mechanisms (Ueno et al., 2020; Wang et al., 2020). Furthermore, neuroscience data suggested that an increased RS-FC between DMN and interoceptive self areas might represent a neural signature of psychological dissociation (Harricharan et al., 2020; van der Kruijs et al., 2014), which is considered a non-voluntary maladaptive form of emotion regulation (Cavicchioli et al., 2021, 2023) well documented among patients with FM (Duarte et al., 2019; Leavitt et al., 2002; Romeo et al., 2022). The increased RS-FC between DMN and interoceptive self areas together with its connection with psychological dissociation among patients with FM might also represent a latent dimension involved in explaining significant comorbidity rates between FM and PTSD/personality disorders (e.g., borderline personality disorder) (Kleykamp et al., 2021), for which dissociation is considered a core clinical feature (Lyssenko et al., 2018; Scalabrini et al., 2017).

On the one hand, moderation analysis did not show a significant effect of studies that excluded FM patients with psychiatric conditions, including MDD. On the other hand, self-report suggested that FM subjects were characterized by a severe depressive symptomatology (i.e., very large ESs) compared to HCs. According to this evidence, meta-analytic results highlighted an increased RS-FC between the DMN and exteroceptive self areas, including auditory and visual cortices. Intriguingly, this neural organization has been considered a neurobiological signature of an active depressive episode (Scalabrini et al., 2020). Specifically, it has been hypothesized that such RS-FC could underpin core phenomenological aspects of depression, namely an altered perception of external world (i.e., exteroceptive areas) tainted and shaped by internally oriented cognition like rumination and increased self-focus attention (i.e., DMN activity) (Northoff, 2007, 2016; Northoff et al., 2011). Accordingly, the current meta-analytic findings could provide a neurobiological underpinning for the co-occurrence between FM and MDD, which is the most prevalent mental disorder in this syndrome (Kleykamp et al., 2021). Following previous considerations concerning mental functioning associated to depressive episodes and self-report findings revealed in FM clinical populations (Fonseca das Neves et al., 2023; Malin et al., 2015; Toussaint et al., 2019), rumination — self-focused intrusive and uncontrollable thought patterns (Brinker and Dozois, 2009; Ingram, 1990; Mor and Winquist, 2002; Nolen--Hoeksema, 1991; A Scalabrini et al., 2022) — should be considered a core maladaptive feature of psychological functioning of FM. Moreover, rumination has been viewed as a prototypical maladaptive emotion regulation strategy (Nolen-Hoeksema et al., 2008) characterized by a cognitive over-control of affective states (Naragon-Gainey et al., 2017). Hence, these considerations and evidence might further support the key role of maladaptive self-regulatory processes of affective states for understanding mind-body suffering of patients with FM (Pinto et al., 2023).

Current findings also showed that specific regions of the pain matrix, namely the PAG and SSAs, played a central role in FM. Particularly, the analyses highlighted a reduced RS-FC between these regions. The PAG, its functional connection with SSAs together with downward projections to spinal dorsal horn neurons modulate pain transmission information (Ossipov et al., 2010). Interestingly, a reduced RS-FC between these regions was significantly associated with relevant clinical features of FM, which included central sensitization symptoms and sleep quality (Harper et al., 2018; Soldatelli et al., 2023). Furthermore, this alteration of RS-FC within the pain matrix represented a neurobiological predictor of responses toward painful stimuli among patients with FM (Harper et al., 2018; Soldatelli et al., 2023). Taken these findings together, areas of the pain matrix extending the topography of the self should be considered additional neurobiological signatures of somatic symptoms recognized as primary diagnostic criteria of FM (Wolfe et al., 2016).

Ultimately, meta-analytic results highlighted that increased intra DMN RS-FC and heightened RS-FC between DMN and interoceptive self areas showed a positive relationship with the intensity of pain reported by patients with FM. This finding might provide neurobiological bases for extending mechanisms involved in core pain symptoms of patients with FM (Wolfe et al., 2016). According to our hypothesis concerning the key role of the self as a foundation for comprehensively clarifying clinical characteristics of FM, the severity of pain symptoms might be viewed as a mind-body experience linked to the degree of self-relatedness or personal relevance for the individual (Northoff, 2016). These considerations might be provisionally in line with empirical investigations of subjective experiences of patients with FM, who reported a sense of "*loss of self*" (i.e., feelings of isolation from external world and others) (Rodham et al., 2010) and a strong identification with a representation of themselves as "*suffering individuals*" (Barker, 2002). Furthermore, current meta-analytic results could be consistent with acceptance and commitment therapy (ACT) framework (Hayes, 2004). Accordingly, it has been posited a key role of *self-as-context* process in explaining painful experiences and its treatment among patients with FM (Ljótsson et al., 2014; Luciano et al., 2014; Yu et al., 2017; Wicksell et al., 2013). The self-as-context captures a sense of self that is not based on the content of one's psychological experiences (e.g., thoughts, feelings, judgments, body sensations) but rather on a sense of taking a perspective on these (e.g., a distinction between one's experiences and the 'I' who notices these experiences) (Hayes et al., 2012; Yu et al., 2016). Following this clinical conceptualization and current meta-analytic findings, the intensity of painful experiences in FM might be viewed in the light of two main maladaptive processes involved in mind-body suffering (Hayes et al., 1996; Kashdan et al., 2006): i) a cognitive fusion or an excessive mental entanglement with painful physical sensations; ii) a rigid self-narrative over-organized around painful body sensations (i.e., conceptualized self) (Hayes et al., 2012). Nevertheless, this hypothesis attempting to integrate neuroscience and clinical results should be empirically tested. Particularly, future RS-FC studies should demonstrate that alterations found in the current meta-analysis would be significantly associated to well-validated measures of cognitive fusion (e.g., cognitive fusion questionnaire; Gillanders et al., 2014), which have been extensively used among patients with FM (e.g., Écija et al., 2020; Luque-Reca et al., 2023). Furthermore, future studies should show how improvements of pain symptoms induced by specific pharmacological and psychotherapeutic treatments for FM would be associated to a reorganization of RS-FC neural activity and, cognitive fusion would be a significant mediator of these therapeutic changes.

Despite these evidence-based considerations, some limitations must be discussed. First, meta-analytic findings showed a large heterogeneity that remained unexplained even controlling for several possible sources of variability. This evidence might suggest the existence of different subgroups of FM associated to distinct etiopathogenic mechanisms (e.g., nociplastic pain, immune alterations) (Andres-Rodriguez et al., 2020; O'Mahony et al., 2021; Sarzi-Puttini et al., 2020). Accordingly, future research should be carried out in order to clarify whether interoceptive and mental self-processing neural networks together with specific areas of the pain matrix might be involved in specific forms of FM, or alternatively, they could represent common neural dimensions associated to core clinical manifestations of FM independently of ethipathogenic mechanisms.

Secondly, the analyses found bias of publication considering the comparison of neural RS-FC between patients with FM and HCs. This evidence might be explained by different sources of bias. First, it has been demonstrated that studies with statistically significant results are more likely to be published than studies that report no significant findings (Dickersin et al., 2005). Furthermore, we included articles written in English, which could be a language bias (i.e., English-language databases and journals are more likely to be searched, which leads to an oversampling of statistically significant studies) (Jüni et al., 2002). An additional bias might be associated to cultural aspects. Indeed, studies were recurrently carried out in USA (N = 4; 38.4%) and Sweden (N = 3; 23.1%). The remaining studies were conducted in western Europe (i.e., Germany, Italy, Spain and United Kingdom; N = 4, 30.8%). Hence, future trans-culture studies are needed to effectively generalize and replicate current alterations of RS-FC among several FM populations.

The original studies did not include clinical control groups. This could represent a further limitation of the current meta-analytic work. On the one hand, it was controlled the effects of the exclusion of comorbid psychiatric conditions on ESs reflecting alterations of RS-FC in FM group and, meta-regression analyses did not find a significant relationship between severity of depressive/anxious symptoms with RS-FC ESs. On the other hand, it is well-established the high co-occurrence rate of lifetime MDD among patients with FM (Kleykamp et al., 2021) and, the current meta-analysis highlighted a neural RS-FC that overlapped with results found among patients with MDD during a depressive episode (Scalabrini et al., 2020). Therefore, future RS-FC studies should compare FM individuals with MDD patients in order to effectively detect common and specific patterns of neural organization associated to each condition. Although the current meta-analysis included FM patients without other chronic pain-related conditions and rheumatic diseases, future neuroscience studies should compare FM subjects with the previously mentioned medical conditions. This is needed in order to further identify core neurobiological features characterizing FM.

Despite these limitations, this is the first study that has quantitatively summarized empirical findings concerning neural RS-FC associated to FM. This is also the first study that has ascribed these results to the nested hierarchical model of self framework, which provides neurobiological and psychological backgrounds for clarifying core mind-body clinical features of FM. Accordingly, an increased RS-FC between the DMN (i.e., mental self) and intero-exteroceptive self layers might be involved in pain experiences and maladaptive regulatory processes of affective states characterizing individuals with FM. These neurobiological dimensions might also be associated to the comorbidity between FM and mental disorders characterized by high internalized negative affectivity. Furthermore, the current results suggested an extension of the topography of nested hierarchical model of self associated to FM, which include specific areas ascribed to the pain matrix and involved in pain modulation. These meta-analytic findings support a synergic implementation of well-supported pharmacological treatments, especially psychopharmacological ones (e.g., antidepressants, serotonin and noradrenaline reuptake inhibitors) (Giorgi et al., 2024), with evidence-based psychotherapeutic programs for the treatment of FM. According to the current findings that have highlighted a key role of brain networks involved in self organization, regulation of affective states and internalizing psychopathological problems, evidence-based psychodynamic programs, especially Dynamic Interpersonal Therapy (Lemma et al., 2010, 2011), and third wave cognitive therapy interventions (i.e., ACT, mindfulness-based stress reduction and mindfulness-based cognitive therapy) should be considered as the gold standard for the treatment of FM. This consideration is based on: i) well-validated therapeutic effects of these interventions in addressing maladaptive self-related (Leonidaki et al., 2020; Hayes et al., 2013; Desbordes, 2019) and emotion regulation (Aminizadeh et al., 2022;

Guendelman et al., 2017; Valdivia-Salas et al., 2010) processes together with internalizing symptoms, especially depressive ones (Bai et al., 2020; Hoge et al., 2021; Fonagy et al., 2020); ii) these evidence-based interventions have been effectively used for the treatment of FM and its core clinical features (Benfante et al., 2022; Eastwood and Godfrey, 2024; Haugmark et al., 2019; Romeo et al., 2019). Furthermore, the efficacy of these intervention should be demonstrated taking into account the neural organization of self and related regulatory processes of affective states considered as key dimensions associated to clinical features of FM.

CRediT authorship contribution statement

Marco Cavicchioli: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Andrea Scalabrini:** Writing – review & editing, Writing – original draft. **Filippo Nimbi:** Writing – review & editing. **Alessandro Torelli:** Writing – review & editing. **Sara Bottiroli:** Writing – review & editing. **Anna Pichiecchio:** Writing – review & editing. **Elena Prodi:** Writing – review & editing. **Cristina Trentini:** Writing – review & editing. **Piercarlo Sarzi-Puttini:** Writing – review & editing. **Federica Galli:** Writing – review & editing.

Data statement

The data that support the findings of this study are available on request from the corresponding author (M.C.).

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.01.048.

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